REMARKS/ARGUMENTS

STATUS OF THE CLAIMS

Claims 1, 3-10, 13-19, 21-56, 61, and 304-308 are pending with entry of this amendment, claims 201-221 being cancelled herein, claims 14-17 having been withdrawn and claims 2, 11-12, 20, 57-58, 62-200, and 222-303 having been cancelled previously. These amendments introduce no new matter and support is replete throughout the specification. These amendments are made without prejudice to renewal of the claims in their original form and are not to be construed as abandonment or dedication of the previously claimed subject matter or agreement with any objection or rejection of record.

Applicants submit that no new matter has been added to the application by way of the above claim amendments. Accordingly, entry of the Amendment is respectfully requested.

As an initial matter, Applicants would like to thank the Examiner and the Supervisory Patent Examiner for the courtesy extended to the undersigned (Monicia Elrod-Erickson) in conducting a telephone interview with the Examiner and the Supervisory Patent Examiner on October 16, 2007, in which the restriction of claims 304-307, the objections to the claims, and the art by Burbaum et al., Walker et al., Ting et al., and also Ladner et al. and Kris et al. with respect to the claim rejections under 35 USC §103 were discussed.

The action of June 14, 2007 included: restriction and alleged constructive election (item 1), rejections for alleged obviousness (items 2-5), and indication of allowable subject matter (item 6). Applicants traverse all rejections and objections for the reasons noted herein.

Applicants note with appreciation the Examiner's indication of allowable subject matter and withdrawal of previous rejections.

THE ELECTION/RESTRICTION REQUIREMENT (ACTION ITEM 1)

The Action alleged that claims 304-307 submitted in the previous response (dated May 3, 2007) were directed to an invention that is independent or distinct from that originally claimed, and that these claims were therefore withdrawn from consideration as being directed to a non-elected invention.

However, as discussed with the Examiner during the interview of October 16, 2007, these claims are in fact directed to an invention originally claimed. The Examiner was reminded that claims 21, 29, 36, and 45 as originally filed were multiply dependent on claims 1 and 2. In a previous Action (mailed December 16, 2005), the Examiner indicated these claims were objected to as being dependent upon a rejected base claim but would be allowable if rewritten in independent form including all the limitations of the base claim and any intervening claims. Applicants amended claims 21, 29, 36, and 45 accordingly, to include the limitations of claim 1 or 2. Then in a telephone interview held regarding the next Action (mailed January 18, 2007), the Examiner indicated the rewritten claims were difficult to read and that separate claims, one incorporating the limitations of claim 1 and another incorporating the limitations of claim 2, would be preferred and would overcome the 112 rejection of the claims for alleged indefiniteness. Accordingly, in the response mailed May 3, 2007, Applicants amended the claims as discussed with the Examiner, amending claims 21, 29, 36, and 45 to include the limitations of claim 1 and introducing new claims 304-307 to include the limitations of claim 2.

Claims 304-307 are thus directed to an invention that was originally claimed and, in fact, one which has already been examined in no less than four previous office actions.

If the Examiner nonetheless wishes to restrict these claims, Applicants respectfully request issuance of a formal restriction requirement to this effect. In addition, in accordance with the Office's policy regarding the new claims and continuation rules, Applicants respectfully request that any restriction requirement issued include an express waiver of the requirement that the non-elected invention has not been examined to permit Applicants to file a divisional application for the non-elected invention and the approval of the Technology Center director (see, for example, Item C7 in the Office document "Questions and Answers:

Claims and Continuations Final Rule" updated October 10, 2007 and available at http://www.uspto.gov/web/offices/pac/dapp/opla/presentation/ccfrfaq.pdf).

OBJECTIONS TO THE CLAIMS

In the "Disposition of Claims" section of the Office Action Summary, claims 26-28 and 33-46 were listed as objected to, although no grounds for the objection were presented in the Action. In the interview of October 16, 2007, the Examiner indicated that claims 26-28, 33-35, 37-44, and 46 were objected to as dependent on withdrawn and rejected claims. As noted above, Applicants do not agree that claims 304-307 should be withdrawn. If a restriction requirement is issued and claims 304-307 are not elected and are cancelled, claims 26-28, 33-35, 37-44, and 46 will be amended accordingly to obviate the objection.

The Examiner further indicated there were no grounds of objection to claims 36 and 45. Accordingly, Applicants respectfully request that these claims be allowed.

THE CLAIMS ARE NOT OBVIOUS (ACTION ITEMS 2-5)

Item 2

Claims 1, 3-5, 7-8, and 308 were rejected for alleged obviousness under 35 USC 103(a) over Burbaum et al. in view of Walker et al. further in view of Ting et al. Applicants respectfully traverse these rejections.

As recently reaffirmed by the Supreme Court in KSR International Co. v. Teleflex, Inc. (550 U.S. __, 82 USPQ2d 1385 (2007)), the appropriate standard for analyzing questions of obviousness is that

> "the scope and content of the prior art are determined, differences between the prior art and the claims at issue are analyzed and the level of ordinary skill in the pertinent art is resolved. Against this background the obviousness or non-obviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unresolved needs, failure of others, etc. might be utilized to give light to the circumstances surrounding the origin of the subject matter to be patented.
>
> *Id.* quoting Graham v. John Deere of Kansas City 383 U.S. 1, 17-18.

This Graham v. John Deere standard has long been interpreted by the Office to mean that three requirements must be met for a *prima facie* case of obviousness. First, the prior art

reference(s) must teach or suggest all of the limitations of the claims (M.P.E.P § 2143.03). Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention (M.P.E.P. § 2143.01). Third, a reasonable expectation of success is required (M.P.E.P. § 2143.02).

A recent memorandum (dated May 3, 2007) from the Deputy Commissioner to the Technology Center Directors regarding the KSR/Graham standard reiterates that, while "The Court rejected a rigid application of the 'teaching, suggestion, or motivation' (TSM) test" (emphasis added), it "did not totally reject the use of 'teaching, suggestion, or motivation' as a factor in the obviousness analysis." The memo concludes that "in formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed" (emphasis added). Similarly, guidelines for examination recently published in the Federal Register (vol. 72 no. 195 p. 57526) also highlight the need for "clear articulation of the reason(s) why the claimed invention would have been obvious."

Application of the KSR/Graham standard in the present case indicates that the claims at issue are not obvious. For example, no reason why a person of ordinary skill in the art would have combined the teachings of Burbaum, Walker, and Ting has been established. Namely, as discussed with the Examiner, no reason – based on the prior art rather than on Applicants' disclosure – for introducing the compounds of Burbaum into a cell has been identified. Applicants note that Burbaum designed substrates for secreted reporter enzymes, to be provided in cell media (see, e.g., column 8 lines 12-15, column 21 lines 39-45, and column 23 lines 5-19 of Burbaum). Walker describes caged peptides that inhibit calmodulin/MLCK activity and is thus focused on control of protein activity; there is no suggestion from Walker that other compounds should be injected into cells to detect activity inside the cell as the Action alleges. In Ting, there is no suggestion that the constructs of Ting can be controlled by caging, nor is there any mention of the desirability of such control.

In addition, Applicants note with respect to claim 308 that the combination of Burbaum, Walker, and Ting fails to teach all the limitations of the claim. For example, claim 308 specifies that an induced conformational change in the first caging groups permits the

enzyme to act upon the substrate. Burbaum and Walker teach photosensitive caging groups, and, as noted above, Ting does not speak to caging at all (the conformational change mentioned by Ting occurs in the protein construct, not in any caging group).

In summary, Applicants appreciated the possibility of and the advantages to introducing a caged enzyme sensor into a cell to controllably assay activity of an intracellular enzyme. The prior art, on the contrary, does not teach or suggest the desirability of caged intracellular enzyme sensors. Motivation to combine the teachings of Burbaum, Walker, and Ting and expectation of success have not been established, and the combination does not teach a least a conformational change in the caging groups. Accordingly, Applicants respectfully request the rejections be reconsidered and withdrawn.

Item 3

Claims 1, 3-6, 9, 10, 18, 21, 23-25, 29-32, and 308 were rejected for alleged obviousness under 35 USC 103(a) over Ting et al. in view of Burbaum et al. further in view of Walker et al. and Ladner et al. Applicants respectfully traverse these rejections.

Again, three requirements must be met for a *prima facie* case of obviousness: the prior art reference(s) must teach all of the limitations of the claims, a reason must be identified for combining the teachings to produce the claimed invention, and a reasonable expectation of success is required.

These requirements are not met by the combination of Ting, Burbaum, Walker, and Ladner.

As discussed with the Examiner, no reason to combine the teachings of Ting, Burbaum, Walker, and Ladner by including in the composition of Ting the substrate being caged as taught by Burbaum and Walker with protein production *in vitro* as taught by Ladner, as suggested in the Action, has been established.

As a first consideration, one of skill would not be motivated to combine the references as suggested because they can not be combined as suggested. As discussed with the Examiner, the caged substrates of Burbaum and the caged peptides of Walker are chemically synthesized *in vitro*, while the fluorescent protein constructs taught by Ting are expressed *in vivo* in a cell from recombinant nucleic acid constructs. As discussed with the Examiner, the protein constructs of Ting are simply too large to be synthesized by current *in*

vitro peptide synthesis techniques such as those used by Walker to produce caged peptides. See, e.g., the attached Appendix, which includes Genbank records for three constructs of Ting, from which the polypeptide products are calculated to be 586, 591, and 777 amino acid residues in size, and a review by Guzman et al. which states that "Chemical synthesis is a viable technique for the production of small to medium-size peptides ranging from about 5 to 80 residues" (emphasis added; page 280, third paragraph). One of skill in the art would thus not consider applying the caging techniques of Walker or Burbaum to the large protein constructs of Ting. Also as discussed with the Examiner, although Ladner teaches protein synthesis *in vitro* and *in vivo* as noted in the Action, the *in vitro* synthesis of Ladner is ribosomal synthesis, not chemical synthesis, and thus still does not provide a route to caging the constructs of Ting using the *in vitro* chemical synthesis techniques of Burbaum or Walker. (See, e.g., paragraphs 803-809 of Ladner that describe construction of synthetic genes with ribosome binding sites and tac promoters, making it clear that the "*in vitro*" expression of paragraph 811 cited in the Action is *in vitro* ribosomal translation, not *in vitro* chemical synthesis.)

In addition, a *prima facie* case of obviousness can not be established where the proposed combination of references changes the principal of operation of the prior art invention being modified (M.P.E.P. § 2143.01). As noted above, the protein constructs described by Ting are produced by expression in a cell. Combining one of these constructs with the teachings of Burbaum, Walker, and Ladner would require the protein construct to be chemically synthesized and/or synthesized outside the cell and then reintroduced into the cell, and this would require modification of the principal of operation of this construct as described.

More importantly, and as discussed with the Examiner, even if the constructs of Ting could be caged as described in Burbaum or Walker, no reason for doing so based on the prior art rather than Applicants' disclosure has been established. The Action alleges that "it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the composition of Ting et al., the substrate being caged as taught by Burbaum et al., in order to provide injection into a cell and give time to allow the substrate to distribute evenly so normal cell activity can be detected as taught by Walker et al." However,

Applicants note that the constructs of Ting are already in the cell, and, in fact, Ting states they are produced *in vivo* specifically to avoid the need to introduce them into a cell (see page 15003, first paragraph, of Ting). The rationale Walker states in their introductory paragraph for caging their peptides is to avoid problems created by injecting inhibitors into cells - but again, as noted, the constructs of Ting are already *in* cells. There is simply no reason why one would take a construct of Ting out of the cell by making it *in vitro* and caging it and then put it back into the cell to avoid problems caused by introducing it into the cell, as the Action suggests doing.

Further, no motivation based on the art for caging a sensor inside a cell has been provided at all. As noted above, Ting does not suggest the desirability or possibility of caging their constructs; Walker describes caging an inhibitor of proteins essential to cell function and focuses on control, not detection, of protein activity (and Applicants note that sensors, unlike inhibitors of key cellular proteins, are not necessarily expected to need caging to keep them from interfering with cell function); and Burbaum does not speak to events inside cells at all.

No reason to combine the teachings of Ting, Burbaum, Walker, and Ladner to produce a caged sensor like those of the present invention has been identified. The Examiner's argument that the references be combined thus involves an improper hindsight reconstruction of the invention.

Moreover, a reasonable expectation of success has not been demonstrated. For example, as noted above, the protein constructs described in Ting are produced by expression in a cell, while the caged substrates of Burbaum and the caged peptides of Walker are produced by *in vitro* chemical synthesis; no route to successful production of caged sensors has been identified by the Action. In addition, for claims as detailed below, there is no reasonable expectation of success since the suggested combination does not result in the present invention.

The combination of Ting, Burbaum, Walker, and Ladner fails to teach all the limitations of the claims, particularly claims 21, 23-25, and 30. With respect to claim 21 (and, similarly, claim 304), Applicants note that, as discussed with the Examiner, the constructs of Ting actually operate in the reverse fashion from the claimed sensors. As

illustrated in Figure 1a of Ting, the YFP and GFP moieties do not interact when the substrate is not phosphorylated, and do interact when the substrate is phosphorylated. This is the opposite of the sensor of claim 21, which specifies that the first label and the second label or the quencher interact when the substrate is not phosphorylated and do not interact when the substrate is phosphorylated. The combination of Ting, Burbaum, Walker, and Ladner thus fails to teach all the limitations of claim 21. Additional points of distinction are present in the dependent claims, but because independent claim 21 (and, similarly, claim 304) is not anticipated, it is not necessary to address each additional point. Applicants also note that, with respect to claim 30, the combination fails to teach at least location of the one or more caging groups on a residue phosphorylated by the kinase, and with respect to claim 308, the combination fails to teach at least an induced conformational change in the first caging groups (see also claim 5, which specifies a different class of caging group, where the groups are removed to alleviate inhibition).

Because no reason for combining the teachings of Ting, Burbaum, Walker, and Ladner has been established, because there is no reasonable expectation of success, and because the combination does not include all the limitations of the claims as indicated, the rejections should be withdrawn.

Item 4

Claims 13, 19, 22, 30, and 61 were rejected for alleged obviousness under 35 USC 103(a) over Ting et al. in view of Burbaum et al. further in view of Walker et al., Ladner et al., and Kris et al. Applicants respectfully traverse these rejections.

The combination of Ting, Burbaum, Walker, Ladner, and Kris does not meet the requirements for a *prima facie* case of obviousness.

First, the combination does not teach all the limitations of at least claims 19, 22, and 30. Regarding claim 19, Kris is alleged to "teach a polypeptide substrate (par. 18-19), wherein the one polypeptide comprises a first label and substrate for kinase (labeled antibodies bind to substrate, and therefore a single polypeptide comprises the substrate and first label, par. 256-258)." As discussed with the Examiner, however, the substrate and the antibody of Kris are in fact two separate molecules. The fact that the labeled antibody can bind the phosphorylated substrate does not mean that the antibody and substrate are included

on a single polypeptide. Whether they are bound to each other or not, they are still two distinct polypeptides and thus fail to meet the limitations of claim 19, which specifies that one polypeptide comprises the first label and the substrate.

Also with respect to claim 19, the Action alleges that Kris teaches the first label located at the tyrosine residue. However, Applicants note that the label of Kris is located on the antibody; the label not found on the substrate at all, much less at the tyrosine residue of the substrate. Furthermore, although the Action alleges that the label "exhibits a first signal when the residue is not phosphorylated and the second signal when the" residue is phosphorylated, Applicants note that the signal from the label is not responsive to the state of the substrate.

With respect to claims 22 and 30, the combination of Ting, Burbaum, Walker, Ladner, and Kris fails to teach at least location of the one or more caging groups on a residue phosphorylated by the kinase. Further, with respect to claim 22 which depends from claim 21, as described above, Ting (and thus the combination of Ting, Burbaum, Walker, Ladner, and Kris) fails to teach a sensor such as that of claim 22 in which the labels interact when the substrate is not phosphorylated and do not interact when the substrate is phosphorylated.

The combination of Ting, Burbaum, Walker, Ladner, and Kris thus does not teach all the limitations of the indicated claims. Moreover, with respect to all the claims, motivation to combine the teachings of the references is lacking. As described in some detail above and as discussed with the Examiner, motivation for combining the teachings of Ting, Burbaum, Ladner, and Walker is clearly lacking; motivation for adding the teachings of Kris is similarly lacking. Further, Applicants note that the rationale for combining the teachings cited in the Action is unclear (namely, it is not clear why a protease as taught by Kris would be included with the kinase substrates of Ting). In addition, there is no reasonable expectation of success. Applicants respectfully request the rejections be withdrawn.

Item 5

Claims 47-56 were rejected for alleged obviousness under 35 USC 103(a) over Ting et al. in view of Burbaum et al. further in view of Walker et al., Ladner et al., and Fischer et al. Applicants respectfully traverse.

The combination of Ting, Burbaum, Walker, Ladner, and Fischer does not meet the requirements for a *prima facie* case of obviousness.

With respect to claims 50 and 55, the combination does not teach all the limitations of the claims. For example, the combination fails to teach at least covalent attachment of a cellular or subcellular delivery module that is reversible by light.

In addition, with respect to all the claims, motivation to combine the teachings of the references is lacking. As described in some detail above and as discussed with the Examiner, motivation for combining the teachings of Ting, Burbaum, Ladner, and Walker is lacking; motivation for combining the teachings of all five references is similarly lacking. In addition, there is no reasonable expectation of success. Applicants respectfully request the rejections be withdrawn.

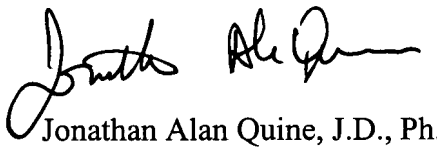
CONCLUSION

In view of the foregoing, Applicant(s) believe(s) all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone Monicia Elrod-Erickson at (510) 337-7871 to schedule an interview.

QUINE INTELLECTUAL PROPERTY LAW GROUP
P.O. BOX 458, Alameda, CA 94501
Tel: 510 337-7871
Fax: 510 337-7877
PTO Customer No.: **22798**
Deposit Account No.: **50-0893**

Respectfully submitted,



Jonathan Alan Quine, J.D., Ph.D.,
Reg No. 41,261
For Monicia Elrod-Erickson,
Reg. No. 51,651

Attachments:

1) A petition to extend the period of response for two months;
2) A transmittal sheet;
3) A fee transmittal sheet;
4) An Appendix; and,
5) A receipt indication postcard.